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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/627,140	07/25/2003	David W. Piotrowski	01085.US1	3914

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EXAMINER

HUANG, EVELYN MEI

ART UNIT	PAPER NUMBER
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1625

DATE MAILED: 01/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/627,140

Applicant(s)

PIOTROWSKI ET AL.

Examiner

Evelyn Huang

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 August 2004.
2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-36 is/are pending in the application.
4a) Of the above claim(s) 12-25 is/are withdrawn from consideration.
5) ☒ Claim(s) 1-4, 6-11 and 26 is/are allowed.
6) ☒ Claim(s) 27-36 is/are rejected.
7) ☒ Claim(s) 5 is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-36 are pending.

Election/Restrictions

2. During a telephone conversation with Ms. Hoseley on 4-7-2004 a provisional election was made with traverse to prosecute the invention of Group III, claims 1-11, 26 in part, drawn to a compound wherein the Azabicyclo is of formula III or IV. Claims of Groups I, II, IV-VII are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicants submit that the azabicyclo heptane, octane and nonane as recited in formula 1 are structurally closely related because they all contain the nitrogen atom at the bridgehead, and a search for these moieties would not be burdensome.

On the contrary, the compound of these groups are chemically, structurally and patentably distinct from the compound of Group III. They have acquired a separate status in the art as shown by their different classification. A reference anticipating one group of compound would not render obvious the compounds of the other groups. The search is not co-extensive and is burdensome. Since the search required for one group is not required for the other groups, restriction for examination purposes as indicated is proper.

3. The examiner has required restriction between product and process claims, where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04.

Accordingly, the restriction between the product and the method is withdrawn. Claims 27-36 are hereby rejoined.

Claim Objections

4. The objection for Claims 1-11, 26 for containing non-elected subject matter is withdrawn in view of the amendment deleting the non-elected subject matter from these claims.

Claim Rejections - 35 USC § 112

5. The rejection for Claims 1-7, 10, 11, 26 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn because the amendment has obviated the rejection.

Duplicate Claims

6. Claim 5 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 4. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27, 28, 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed

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invention. The antipsychotic agent recited in claims 27, 31 reaches out to as yet unidentified antipsychotic agents, the description of which is not found in the specification. The method for treating a disease or condition in a mammal, wherein the mammal would receive symptomatic relief from the administration of an $\alpha 7$ nicotinic acetylcholine receptor agonist reaches out to as yet unidentified diseases/disorders, a description of which is not found in the specification.

Claim Rejections - 35 USC § 112(1)

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. The following evaluation factors have been considered.

a. *Nature of the invention.*

The instant invention is drawn to an azabicyclo compound for use as an $\alpha 7$ nicotinic acetylcholine receptor agonist in the treatment of a disease or condition, in combination with antipsychotic agent(s). The diseases are recited on pages 9-10 of the specification..

b. *State of the prior art and the level of the skilled in the art.*

Different subclasses, including the $\alpha 7$ nicotinic acetylcholine receptor, have been shown to exist. Agonists and antagonists of nicotinic receptors are known (Holladay, J. Med. Chem. 1997, 40:4169; page 4171, Table 1). The instant compound, however, does not resemble any of the known agonists of nicotinic acetylcholine receptor.

While the possible function of $\alpha 7$ nicotinic acetylcholine receptor includes cognition, neuroprotection and sensory gating (page 4171, Table 1), the exact role of $\alpha 7$ nicotinic acetylcholine receptor is still under investigation and has not been fully established (page 4173, column 1).

The skilled in the nicotinic acetylcholine receptor agonist art is high.

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c. *Predictability/unpredictability in the art.*

The high degree of unpredictability is well recognized in the nicotinic acetylcholine receptor art. A slight modification of the compound would lead to profound changes in its biological activity as evidenced in the very different affinities exhibited by structurally similar compounds (reviewed on page 4183). One of ordinary skill in the art therefore would have no basis to extrapolate the results to compounds structurally removed from the tested compounds. Drug-drug interaction, i.e. synergism or antagonism, is well-known in the art, especially among compounds of diverse structures, having different chemical and physical properties, acting via different modes of mechanisms. The effects of a combination of drugs are therefore highly unpredictable.

d. *Amount of guidance/working examples.*

The preparation of the example compounds is described.

The assay for measuring the EC₅₀ of $\alpha 7$ nicotinic acetylcholine receptor agonist activity is described and the results described as 'The examples of the present invention have EC₅₀ values between 171 nM and 366 nM' (page 90 of the specification). The procedure for determining the binding constants is found on page 90 of the specification. No data on the binding constants are shown.

An example of a composition comprising the inventive compound and one or more anti-psychotic agents, and/or the method of using the inventive compound in combination of other anti-psychotic agent(s) has not been described.

e. *The breadth of the claims.*

Applicant's assertion that all the structurally diverse compounds embraced the generic claims (especially those with multiple substituents further substituted with optionally substituted ring moieties) would be effective $\alpha 7$ nicotinic acetylcholine receptor agonists, and would be useful in combination with any anti-psychotic agent(s) does not commensurate with the scope of the objective enablement, especially in view of the high degree of unpredictability in the art, the limited working examples directed to specific compounds and the absence of working examples of a composition comprising multiple active ingredients (paragraphs c, d above).

f. *Amount of undue experimentation.*

Since insufficient teaching and guidance are provided by the specification (paragraphs c-d above), one of ordinary skill in the art, even with high degree of skill, would not be able to use the compounds as claimed without undue experimentation.

Allowable Subject Matter

9. Claims 1-4, 6-11, 26 are allowed.

Piotrowski (US 2003/02079130) discloses an azabicyclic-substituted heteroaryl compound similar to the instant. Piotrowski, however, only teaches that the amido carbonyl is attached to the carbon atom of the 5-membered nitrogen containing heteroaryl, whereas the amido carbonyl is attached to the nitrogen of the pyrrolyl or pyrazolyl in the instant compound. Motivation to modify Piotrowski's compound to arrive at the instant is lacking.

Walker (US 2003/0153595, the US equivalent of WO 03/029252, PTO-1449) discloses an azabicyclic-substituted heteroaryl compound similar to the instant. Walker, however, only teaches that the amido carbonyl is attached to the carbon atom of the bicyclic nitrogen containing heteroaryl, whereas the amido carbonyl is attached to the nitrogen of pyrrolyl or pyrazolyl fused to a 6-membered ring in the instant compound. Motivation to modify Walker's compound to arrive at the instant is lacking.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

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however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Huang whose telephone number is 571-272-0686. The examiner can normally be reached on Tuesday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Evelyn Huang

Primary Examiner

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